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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,565	02/08/2006	Edward L.G. Pryzdial	701826-57320	4718

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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,565	PRYZDIAL, EDWARD L.G.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *2,7-9,12,13,18,19 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,10,11,14-17 and 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/3/05, 11/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group IV, drawn to a method of accelerating blood clot dissolution comprising administering Factor Xaγ or a pharmaceutical composition comprising Factor Xaγ, in the reply filed on 04/17/2008 is acknowledged. Applicant's election without traverse of the condition, thrombosis, the fibrolytic agent, tissue plasminogen activator, and the thrombin inhibitor, heparin, in the reply filed on 04/17/2008 is also acknowledged. The elected invention and species read on claims 1, 3-6, 10, 11, 14-17 and 20-23; claims 2, 7-9, 12, 13, 18, 19 and 24 are withdrawn for pertaining to a non-elected invention or species.

Claim Objections

2. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 3 is drawn to a method of administering Factor Xaγ to a subject with the condition thrombosis. Claim 4, which depends on claim 3, is drawn to a method of administering Factor Xaγ to a subject that is susceptible to thrombosis as a prophylactic. Subjects who are susceptible to thrombosis and in need of a prophylactic measure are not a narrower or limiting scope of subjects having the condition and in need of treatment.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007). Claims 20-22 are drawn to pharmaceutical compositions comprising Factor Xaγ and claim 23 is drawn to a pharmaceutical composition further comprising tissue plasminogen activator and/or heparin. Page 7, lines 1-7 of the specification state that Factor Xa bound to procoagulant phospholipid (proPL) and cleaved by plasmin (PN) yields three fragments with molecular weights of 33, 13 and 3 kD which are collectively referred to as Factor Xaγ. The specification states that the presence of proPL during cleavage is critical for the formation of Factor Xaγ. Grundy *et al.* teach a that PN cleavage of Factor Xa under phospholipid binding conditions yields three fragments, two of which are 33 and 13 kD (Figure 1). Grundy *et al.* also teach that these fragments have exposed C-terminal lysine residues, that they play a role in fibrinolysis (or blood clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in enhanced plasmin generation (p. 6294, col. 1). Grundy *et al.* teach compositions comprising these fragments, Factor Xaγ33/13, as well as compositions further comprising t-PA (p. 6294, col. 1). Grundy *et al.* do not explicitly state that these compositions are pharmaceutical compositions for accelerating blood clot dissolution. Given that the compositions taught by the prior art of Grundy *et al.* are structurally identical to the claimed composition, the prior art of Grundy *et al.* inherently meet this functional limitation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 3-6, 10, 11, 14 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007) in view of Gladstone *et al.* (*CNAJ*, **2001**, *165*, 311-7). Claims 1, 5, 6, 10 and 11 are drawn to methods of accelerating blood clot dissolution in a subject in need thereof by administering Factor Xaγ, claims 3 and 4 require that the condition is thromobosis, and claims 14 and 17 further comprise administering tissue plasminogen activator. Page 7, lines 1-7 of the specification state that Factor Xa bound to procoagulant phospholipid (proPL) and cleaved by plasmin (PN) yields three fragments with molecular weights of 33, 13 and 3 kD which are collectively referred to as Factor Xaγ. The specification states that the presence of proPL during cleavage is critical for the formation of Factor Xaγ. Grundy *et al.* teach a that PN cleavage of Factor Xa under phospholipid binding conditions yields three fragments, two of which are 33 and 13 kD (Figure 1). Grundy *et al.* also teach that these fragments have exposed C-terminal lysine residues, that they play a role in fibrinolysis (or blood clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in enhanced plasmin generation (p. 6294, col. 1). Grundy *et al.* teach compositions comprising these fragments, Factor Xaγ33/13 (p. 6294, col. 1). Grundy *et al.* do not explicitly state that

these compositions are used in a method for accelerating blood clot dissolution. Gladstone *et al.* teach that t-Pa administration can be used to treat stroke thrombosis. It would have been obvious to the skilled artisan to administer the Factor Xaγ taught by Grundy *et al.* to subjects having thrombosis. The skilled artisan would have been motivated to do so in light of the teaching of Gladstone *et al.* that t-Pa can be used to treat thrombosis and the teaching of Grundy *et al.* that Factor Xaγ accelerates t-Pa. There would have been a reasonable expectation of success given that Grundy *et al.* teach that Factor Xaγ leads to enhanced plasmin generation. With respect to claim 14, it would have been further obvious to administer both t-Pa and Factor Xaγ given that they both contribute to the fibrinolysis process. With respect to claim 17, it is obvious to optimize the mode of administration through routine experimentation. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

7. Claims 1, 3-6, 10, 11, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grundy *et al.* (*Biochem.*, **2001**, *40*, 6293-6302, citation 1 on the Information Disclosure Statement filed 11/28/2007) in view of Llevadot *et al.* (*JAMA*, **2001**, *286*, 442-9). Claims 1, 5, 6, 10 and 11 are drawn to methods of accelerating blood clot dissolution in a subject in need thereof by administering Factor Xaγ, claims 3 and 4 require that the condition is thromobosis, and claims 15 and 16 further comprise administering heparin. Page 7, lines 1-7 of the specification state that Factor Xa bound to procoagulant phospholipid (proPL) and cleaved by plasmin (PN) yields three fragments with molecular weights of 33, 13 and 3 kD which are collectively referred to as Factor Xaγ. The specification states that the presence of proPL during cleavage is critical for the formation of Factor Xaγ. Grundy *et al.* teach a that PN cleavage of

Factor Xa under phospholipid binding conditions yields three fragments, two of which are 33 and 13 kD (Figure 1). Grundy *et al.* also teach that these fragments have exposed C-terminal lysine residues, that they play a role in fibrinolysis (or blood clot dissolution) and that they accelerate tissue plasminogen activator (t-PA) resulting in enhanced plasmin generation (p. 6294, col. 1). Grundy *et al.* teach compositions comprising these fragments, Factor Xaγ33/13 (p. 6294, col. 1). Grundy *et al.* do not explicitly state that these compositions are used in a method for accelerating blood clot dissolution. Llevadot *et al.* teach that t-Pa administration can be used to treat myocardial infarction thrombosis. It would have been obvious to the skilled artisan to administer the Factor Xaγ taught by Grundy *et al.* to subjects having thrombosis. The skilled artisan would have been motivated to do so in light of the teaching of Llevadot *et al.* that t-Pa can be used to treat thrombosis and the teaching of Grundy *et al.* that Factor Xaγ accelerates t-Pa. There would have been a reasonable expectation of success given that Grundy *et al.* teach that Factor Xaγ leads to enhanced plasmin generation. With respect to claims 15 and 16, it would have been further obvious to administer both Factor Xaγ and heparin given that Llevadot *et al.* also teach that heparin can be used to treat thrombosis. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 3-6, 10, 11, 14-17 and 20-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 11/451,959. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 4-6 and 8 of copending Application No. 11/451,959, which are drawn to a method of accelerating blood clot dissolution by administering a 33 KD fragment of Factor Xa comprising a C-terminal lysine, a 13 KD fragment of Factor Xa comprising a C-terminal lysine, a heterodimer comprising the 33 and 13 KD fragments of Factor Xa and any one or a combination thereof, respectively, anticipate instant claims 1, 5, 6, 10, 11 and 20-22. Claim 2 of copending Application No. 11/451,959 is drawn to a method of accelerating blood clot dissolution in a subject experiencing thrombosis. Thus, claim 2 of copending Application No. 11/451,959 in combination with claims 4-6 and 8 of copending Application No. 11/451,959, renders instant claims 3 and 4 obvious. Claim 9 of copending Application No. 11/451,959 is drawn to a method of accelerating blood clot dissolution comprising administering a Factor X derivative in combination with tissue plasminogen activator. Thus claim 9 of copending Application No. 11/451,959, in combination with claims 4-6 and 8 of copending Application No. 11/451,959, renders instant claims 14 and 23 obvious. Claim 12 of copending Application No. 11/451,959 is drawn to the administration of the Factor

X derivative by a variety of means that are identical to those recited in instant claim 17. Thus, claim 12 of copending Application No. 11/451,959, in combination with claims 4-6, 8 and 9 of copending Application No. 11/451,959, renders instant claim 17 obvious. Claim 11 of copending Application No. 11/451,959 is drawn to a method of accelerating blood clot dissolution comprising administering a Factor X derivative in combination with heparin. Thus claim 11 of copending Application No. 11/451,959, in combination with claims 4-6 and 8 of copending Application No. 11/451,959, renders instant claims 15, 16 and 23 obvious. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 9:00 A.M. to 3:00 P.M.

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb